REMARKS

Claims 11-13, 18-21, 30-31, 40-48, 51-52, and 75-90 are pending in this application.

Claims 1-10, 25-29, 38-39, and 56, have been canceled without prejudice or disclaimer. Claims 14-17, 22-24, 32-37, 49-50, 53-55, and 57-74, have been withdrawn from consideration as being drawn to a non-elected invention. Claims 11-13, 30-31, and 40-48, have been amended. Claims 75-90 have been newly added. Support for claims 11-13, 30-31, and 40-48 as amended and new claims 75-90, can be found throughout the specification, Examples, and claims as originally filed. No new matter has been added.

Regarding Applicants claim for priority, attached hereto is an English language translation of PCT/JP0204084.

In view of the remarks set forth herein, further and favorable consideration is respectfully requested.

I. At page 3, item 3, of the Official Action, the Examiner advises that should claims 1-5, 40 and 43 be found allowable, then claims 7-10, 25-29, 41-42 and 45 will be objected to as being a substantial duplicate thereof.

Claims 1-10 and 25-29 have been canceled without prejudice or disclaimer. Claims 40-43 and 45 have been amended. It is submitted that none of the pending claims are substantial duplicates.

II. At page 4, item 5, of the Official Action, claims 11-13 and 40-48 have been rejected under 35 USC § 101, because the claimed invention is directed to non-statutory subject matter.

In view of the following, this rejection is respectfully traversed.

Responsive to the Examiner's rejection, claims 11-13 and 40-48 have been amended to recite the term "isolated." Accordingly, it is submitted that claims 11-13 and 40-48 are directed to statutory subject matter within the meaning of 35 USC § 101. Thus, the Examiner is respectfully requested to withdraw this rejection.

III. At page 4, item 7, of the Official Action, claims 13 and 47have been rejected under 35 USC § 112, second paragraph, as being indefinite.

The Examiner asserts that there is insufficient antecedent basis in claims 1 and 7 for the limitation "Flk-1" appearing in claims 13 and 47, respectively.

In view of the following, this rejection is respectfully traversed.

Claim 7 has been canceled without prejudice or disclaimer. Claims 13 and 47 have been amended to be dependent on claims having sufficient antecedent basis for the limitation "Flk-1."

It is submitted that claims 13 and 47 are clear and definite within the meaning of 35 USC § 112, second paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. At page 5, item 8, of the Official Action, claims 28-31 have been rejected under 35 USC § 112, second paragraph, as being indefinite.

The Examiner asserts that it is not clear what is meant by an antibody having specific affinity for a gene encoding the marker protein.

In view of the following, this rejection is respectfully traversed.

Claims 28-29 have been canceled without prejudice or disclaimer. Claims 30-31 have been amended to be dependent on claims 75 and 76, respectively.

Accordingly, it is submitted that claims 30-31 are clear and definite within the meaning of 35 USC § 112, second paragraph. Thus, the Examiner is respectfully requested to withdraw this rejection.

V. At page 5, item 9, of the Official Action, claims 1-10, 25-31, 38-39, and 56, have been rejected under 35 USC § 112, second paragraph, as being incomplete for omitting essential steps.

The Examiner asserts the claims omit how to use the substances, how to select cells, or how to fractionate cells.

Claims 1-10, 25-29, 38-39, and 56, have been canceled without prejudice or disclaimer and have been rewritten as new claims 75-90. Claims 30-31 have been amended to be dependent on claims 75 and 76, respectively.

It is submitted that new claims 75-90 properly recite all essential claim steps.

Accordingly, it is submitted that this rejection with regard to claims 1-10, 25-29, 38-39, and 56, is rendered moot. It is further submitted that claims 30-31 are clear and definite within the meaning of 35 USC § 112, second paragraph.

Thus, the Examiner is respectfully requested to withdraw this rejection.

VI. At page 5, item 10, of the Official Action, claims 28-31, have been rejected under 35 USC § 112, second paragraph, as being indefinite.

The Examiner asserts that it is unclear what is meant by a method "containing."

Claims 28-29 have been canceled without prejudice or disclaimer. Claims 30-31 have been amended to be dependent on claims 75 and 76, respectively.

Accordingly, this rejection is moot.

VII. At page 6, item 121, of the Official Action, claims 1, 2, 4, and 5, have been rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement.

Claims 1, 2, 4, and 5, have been canceled without prejudice or disclaimer. Accordingly, this rejection is moot.

VIII. At page 8, item 13, of the Official Action, claims 1-3, 7, 8, 11, 25-27, 38, 40-42, and 56, have been rejected under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement.

Claims 1-3, 7, 8, 25-27, 38, and 56, have been canceled without prejudice or disclaimer. The subject matter of these claims appears in new claims 75-90. Dependent claims 11 and 40-42, have been amended to be dependent on new claims 76, 75, 76, and 79, respectively.

New claims 75-76 are directed to a method of separating comprising contacting with an antibody or functional fragment thereof. New claims 77-78 are

directed to a method of identifying comprising contacting isolated mRNA with a probe or primer pair.

In view of the above, it is submitted that the claims are fully enabled within the meaning of 35 USC § 112, first paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IX. At page 12, item 16, of the Official Action, claims 1-13, 18-21, 25-31, 38-48, 51, 52, and 56, have been rejected under 35 USC § 103, as being unpatentable over Ramiya et al., in view of Serup, Oberg-Welsh et al., and Suzuki et al.

The Examiner asserts that it would have been obvious to the skilled artisan to use antibodies directed against c-Met and additional markers, to separate the pancreatic stem cells from the single cell suspension of Ramiya et al with the motivation to separate provided by Serup, Oberg-Welsh et al., and Suzuki et al.

In view of the following, this rejection is respectfully traversed.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under § 103 by (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of nonobviousness.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists;

(2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all the claim limitations. *Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. *See Ex parte Clapp*, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. *Id.* at 974.

A proper case of obviousness under 35 U.S.C. §103, requires that the prior art, as a whole, must suggest the desirability of making the claimed combination and provide a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

The *Dow* court further held that "In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." The court in *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994), held that "A prior art reference may be said to *teach away* when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." The court in *Busch & Lamb, Inc. v. Barnes-*

Hind/Hydro curve, Inc., 796 F.2d 443 (Fed. Cir. 1986), held that "A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered."

Regarding motivation to modify a reference, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *See Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." *In re Mills,* 916 F.2d 680 at 682.

If a proposed modification would render the prior art invention being modified unsatisfactorily for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). In addition, if a proposed modification or combination of prior art references would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 813 (CCPA 1959).

Present claim 75 recites a method of separating a pancreatic stem cell from the pancreas of a mammal, comprising isolating pancreatic cells from the pancreas of a mammal to produce pancreatic cells; contacting the pancreatic cells with at least four antibodies or functional fragments thereof each having specific affinity a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119; and separating the pancreatic stem cells from the pancreatic cells based on antibody binding between the antibodies and the

marker proteins to produce separated cells.

Present claim 76 recites a method of separating a pancreatic stem cell from the pancreas of a mammal, comprising isolating pancreatic cells from the pancreas of a mammal to produce pancreatic cells; contacting the pancreatic cells with at least five antibodies or functional fragments thereof each having specific affinity for a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, TER119, and Flk-1; and separating the pancreatic stem cells from the pancreatic cells based on antibody binding between the antibodies and the marker proteins to produce separated cells.

Present claim 77 recites a method of identifying a pancreatic stem cell of a mammal, comprising isolating mRNA from pancreatic cells of a mammal to produce pancreatic mRNA; contacting the pancreatic mRNA with probes and/or primer pairs having specific affinity for at least four genes each encoding a different corresponding marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119; and separating the pancreatic stem cells from the pancreatic cells based on hybridization between the probe and/or the primer pair and the at least four genes each encoding a different corresponding marker protein to produce identified pancreatic stem cells.

Present claim 78 recites a method of identifying a pancreatic stem cell of a mammal, comprising isolating mRNA from pancreatic cells of a mammal to produce pancreatic mRNA; contacting the pancreatic mRNA with probes and/or primer pairs having specific affinity for at least five genes each encoding a different corresponding marker protein selected from the group consisting of c-

Met, c-Kit, CD45, TER119, and Flk-1; and separating the pancreatic stem cells from the pancreatic cells based on hybridization between the probe and/or the primer pair and the at least five genes each encoding a different corresponding marker protein to produce identified pancreatic stem cells.

Present claims 11-13, 30-31, 40-48, and 79-88, are directly or indirectly dependent on independent claim 75 or 76. Present claims 89 and 90 are directly dependent on independent claims 77 and 78, respectively.

Present claim 18 recites a cloned pluripotent pancreatic stem cell, that shows c-Met$^+$, c-Kit$^-$, CD45$^-$ and TER119$^-$. Present claim 19 recites a cloned pluripotent pancreatic stem cell, that shows c-Met$^+$, c-Kit$^-$, CD45$^-$, TER119$^-$ and Flk-1$^-$.

Present claims 20-21 are dependent on independent claim 18. Claims 51-52 are dependent on independent claim 19.

In view of the following, it is submitted that a *prima facie* case of obviousness has not been established.

Ramiya et al. describes the *in vitro* growth of islets from stem cells where adult islet ductal structures were isolated and cultured. Gene expression was then detected by RT-PCR. Ramiya et al. describe at page 279 that transcripts for insulin I, insulin II, insulin receptor, and hepatocyte growth factor and its receptor c-Met, were detected. The Examiner states at page 13 of the Official Action that "Ramiya et al. do not teach separating or identifying the pancreatic stem cells by using antibodies against c-Met, c-Kit, CD45, TER119, and Flk-1."

Serup describes that the identification of reliable surface markers of pancreatic stem cells is a priority. Serup also states that "Unfortunately, there are no reliable surface markers for pancreatic stem cells; indeed, their very identity has been obscure...some data indicate an emerging profile. A candidate pancreatic stem cell, which is characterized by its expression of the neural stem-cell marker nestin and lack of ... islet- and duct-cell markers, was described...." Serup concludes that there are plenty of obstacles that must be overcome before a viable stem cell based therapy for diabetes is in hand and that there is a need to better understand the development of the endocrine pancreas and stem cells.

Oberg-Welsh et al. describes the expression of protein tyrosine kinases in insulin producing cells and immunoreactivity for the receptor Flk-1. Other receptors identified were the FGFR-4, the IGF-1 receptor, c-Kit and the cytoplasmic tyrosine kinase Jak2. Oberg-Welsh et al. also describes that Trk-A (tyrosine kinase receptor) is expressed in fetal islets.

Suzuki et al. describes flow-cytometric separation and enrichment of hepatic progenitor cells in the developing mouse liver.

It is submitted that a *prima facie* case of obviousness has not been established because (i) there is no motivation supporting the combination of Suzuki et al. with any of Ramiya et al., Serup, and Oberg-Welsh et al. taken alone or together; and (ii) nothing in any of Ramiya et al., Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, teach or suggest all of the limitations of the present claims as required by *Amgen* and *In re Wilson*.

There is no motivation supporting the combination of Suzuki et al. with any of Ramiya et al., Serup, and Oberg-Welsh et al., because Suzuki et al. is concerned with hepatic cells while the remaining references are concerned with pancreatic cells. The skilled artisan reviewing any of Ramiya et al., Serup, and Oberg-Welsh et al. that are concerned with pancreatic cells would have no motivation to look to Suzuki et al. that is concerned with hepatic cells. Likewise, the skilled artisan reviewing Suzuki et al. that is concerned with hepatic cells, would have no motivation to look to any of Ramiya et al., Serup, and Oberg-Welsh et al. that are concerned with pancreatic cells.

Assuming *arguendo*, the combination of Suzuki et al. with Ramiya et al., Serup, and Oberg-Welsh et al. proper, it is submitted that nothing in any of Ramiya et al., Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, teach or suggest all of the limitations of the present claims as required by *Amgen* and *In re Wilson*.

Claim 75 recites the step of contacting the pancreatic cells with at least four antibodies and/or functional fragments thereof each having specific affinity a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119. Claim 76 recites the step of contacting the pancreatic cells with at least five antibodies and/or functional fragments thereof each having specific affinity for a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, TER119, and Flk-1.

None of the references teach or suggest contacting pancreatic cells with at least four antibodies and/or functional fragments thereof each having specific

affinity for a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119 as required by claim 75 and claims dependent therefrom, or contacting pancreatic cells with at least five antibodies and/or functional fragments thereof each having specific affinity a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and Flk-1 as required by claim 76 and claims dependent therefrom.

Claim 77 recites the step of contacting the pancreatic mRNA with probes and/or primer pairs having specific affinity for at least four genes each encoding a different corresponding marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119. Claim 78 recites the step of contacting the pancreatic mRNA with probes and/or primer pairs having specific affinity for at least five genes each encoding a different corresponding marker protein selected from the group consisting of c-Met, c-Kit, CD45, TER119, and Flk-1.

None of the applied references teach or suggest contacting pancreatic cells with probes and/or primer pairs having specific affinity for at least four genes each encoding a different corresponding marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119 as required by claim 77 and claims dependent therefrom, or contacting pancreatic cells with probes and/or primer pairs having specific affinity for at least five genes each encoding a different corresponding marker protein selected from the group consisting of c-Met, c-Kit, CD45, TER119, and Flk-1 as required by claim 78 and claims dependent therefrom.

Ramiya et al. describes at page 279 determining the expression of islet cell-associated markers by islet-producing stem cells (IPSCs) and islet progenitor cells (IPCs) by detecting transcripts for insulin I, insulin II, insulin receptor, hepatocyte growth factor and its receptor C-MET, glucagon, somatostatin, glucose transporter-2 receptor, glutamic acid decarboxylase-67, insulin-like growth factor-I, and insulin-like growth factor-II. Ramiya et al. also describes at page 279, analyzing the expression of genes including regenerating gene-1, PDX-1, β-galactosidase, tyrosine hydroxylase, beta2/neuroD, paired box genes 4 and 6, insulin-related protein 1, and Nkx6.1, from IPSCs and IPCs. From the foregoing, it can be seen that Ramiya et al. describes at least 20 factors. Ramiya et al. does not provide any motivation or suggestion to select C-MET from the 20 described factors.

Serup describes that pancreatic stem cells express the neural stem-cell marker nestin. Serup also recites that there is a lack of established islet and duct-cell markers. At most, Ramiya et al. in view of Serup, suggest nothing more than trying all 21 factors in an attempt to establish islet-cell and duct-cell markers.

Oberg-Welsh et al. describes the receptor Flk-1, FGFR-4, the IGF-1 receptor, c-Kit, the cytoplasmic tyrosine kinase Jak2, and Trk-A. Oberg-Welsh et al. does not provide any motivation or suggestion to select c-Kit from the six described factors, let alone combine it with one factor (C-Met) out of the 20 described by Ramiya et al. At most, Ramiya et al. in view of Serup and Oberg-Welsh et al., suggest nothing more than trying all 27 factors in an attempt to

establish islet-cell and duct-cell markers.

Suzuki et al. describes flow-cytometric separation and enrichment of hepatic progenitor cells in the developing mouse liver, and describes that hematopoietic stem cells were excluded by gating out $CD45^+$ and $TER119^+$. Suzuki et al. does not teach or suggest any pancreatic islet-cell or duct-cell marker.

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success."); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). A finding of obviousness requires that some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g., *Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215

In the present case, none of the applied references, taken alone or together, suggest selecting the claimed markers. Further, none of the references taken alone or together, provide a reasonable expectation of success. In fact, Serup expressly states that "Unfortunately, there are no reliable surface markers for pancreatic stem cells; indeed, their very identity has been obscure..." and that

"there are plenty of obstacles that must be overcome before a viable stem cell based therapy for diabetes is in hand...It underscored the need to better understand the development of the endocrine pancreas and stem cells."

In conclusion, at most, Ramiya et al. in view of Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, suggest nothing more than trying all 27 factors in an attempt to establish islet-cell and duct-cell markers. "Obvious to try" is not the proper standard for patenability.

In view of the foregoing, it is submitted that nothing in Ramiya et al., Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, suggest the presently claimed subject matter within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

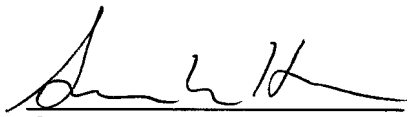
CONCLUSION

In view of the foregoing, Applicant submits that the pending claims are in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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Date: April 13, 2007
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